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ORIGINAL ARTICLE
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Determinants of label non-adherence to non-vitamin K oral anticoagulants in patients with newly diagnosed atrial fibrillation

J Seelig [1,2,3,*†], EM Trinks-Roerdink [4,†], G Chu [5,†], R Pisters [1], LJHJ Theunissen [6], SA Trines [7], L Pos [8], CJHJ Kirchhof [9], SFAMS de Jong [10], FR den Hartog [11], AP van Alem [12], PE Polak [13], RG Tieleman [14], PH van der Voort [15], T Lenderink [16], AM Otten [17], JSSG de Jong [18], YL Gu [19], JGLM Luermans [20], MJHA Kruip [21,22], SAJ Timmer [23], TAC de Vries [1,24], H ten Cate [2,25], GJ Geersing [4], FH Rutten [4], MV Huisman [5,‡], and MEW Hemels [1,3,‡]

[1]Department of Cardiology, Hospital Rijnstate, Rijnstate, Arnhem, the Netherlands; [2]Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht, the Netherlands; [3]Department of Cardiology, Radboud University Medical Centre, Nijmegen, the Netherlands; [4]Department of General Practice, Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht University, Utrecht, the Netherlands; [5]Department of Thrombosis and Haemostasis, Leiden University Medical Centre, Leiden, the Netherlands; [6]Department of Cardiology, Maxima Medical Centre, Eindhoven, the Netherlands; [7]Willem Einthoven Centre for Cardiac Arrhythmia Research and Management, Department of Cardiology, Leiden University Medical Centre, Leiden, the Netherlands; [8]Department of Cardiology, Hospital Group Twente, Hengelo, the Netherlands; [9]Department of Cardiology, Alrijne Hospital Leiderdorp, Leiderdorp, the Netherlands; [10]Department of Cardiology, Elkerliek Hospital, Helmond, the Netherlands; [11]Department of Cardiology, Hospital Gelderse Vallei, Ede, the Netherlands; [12]Department of Cardiology, Haaglanden Medical Centre, The Hague, the Netherlands; [13]Department of Cardiology, St. Anna Hospital, Geldrop, the Netherlands; [14]Department of Cardiology, Martini Hospital, Groningen, the Netherlands; [15]Department of Cardiology, Catharina Hospital, Eindhoven, the Netherlands; [16]Department of Cardiology, Zuyderland Medical Centre, Heerlen, the Netherlands; [17]Department of Cardiology, Gelre Hospitals, Apeldoorn-Zutphen, the Netherlands; [18]Department of Cardiology, onze lieve vrouwe gasthuis, Amsterdam, the Netherlands; [19]Department of Cardiology, Hospital Nij Smellinghe, Nij Smellinghe, Drachten, the Netherlands; [20]Department of Cardiology, Maastricht University Medical Centre, Maastricht, the Netherlands; [21]Anticoagulation Clinic, Star-shl, Rotterdam, the Netherlands; [22]Department of Internal Medicine, Erasmus University Medical Centre, Rotterdam, the Netherlands; [23]Department of Cardiology, Northwest Clinics, Alkmaar, the Netherlands; [24]Department of Cardiology, Amsterdam University Medical Centres location Academic Medical Centre, Amsterdam, the Netherlands; and [25]Department of Internal Medicine, Maastricht University Medical Centre, Maastricht, the Netherlands

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Aims To evaluate the extent and determinants of off-label non-vitamin K oral anticoagulant (NOAC) dosing in newly diagnosed Dutch AF patients.

Methods and results In the DUTCH-AF registry, patients with newly diagnosed AF (<6 months) are prospectively enrolled. Label adherence to NOAC dosing was assessed using the European Medicines Agency labelling. Factors associated with off-label dosing were explored by multivariable logistic regression analyses. From July 2018 to November 2020, 4500 patients were registered. The mean age was 69.6 ± 10.5 years, and 41.5% were female. Of the 3252 patients in which NOAC label adherence could be assessed, underdosing and overdosing were observed in 4.2% and 2.4%, respectively. In 2916 (89.7%) patients with a full-dose NOAC recommendation, 4.6% were underdosed, with a similar distribution between NOACs. Independent determinants (with 95% confidence interval) were higher age [odds ratio (OR): 1.01 per year, 1.01–1.02], lower renal function (OR: 0.96 per ml/min/1.73 m^2, 0.92–0.98), lower weight (OR: 0.98 per kg, 0.97–1.00), active

* Corresponding author. Tel: +31 88 005 7706, Email: jseelig@rijnstate.nl
† S.J., T.-R.E.M. and C.G. are joint first authors.
‡ H.M.V. and H.M.E.W. are joint project leaders of DUTCH-AF.

malignancy (OR: 2.46, 1.19–5.09), anaemia (OR: 1.73, 1.08–2.76), and concomitant use of antiplatelets (OR: 4.93, 2.57–9.46). In the 336 (10.3%) patients with a reduced dose NOAC recommendation, 22.9% were overdosed, most often with rivaroxaban. Independent determinants were lower age (OR: 0.92 per year, 0.88–0.96) and lower renal function (OR: 0.98 per ml/min/1.73 m^2, 0.96–1.00).

Conclusion In newly diagnosed Dutch AF patients, off-label dosing of NOACs was seen in only 6.6% of patients, most often underdosing. In this study, determinants of off-label dosing were age, renal function, weight, anaemia, active malignancy, and concomitant use of antiplatelets.

Keywords Atrial fibrillation • Anticoagulants • Off-label use • Prospective studies • Registries

Introduction

Oral anticoagulants (OACs) are used for stroke prevention in atrial fibrillation (AF). For most AF patients, non-vitamin K oral anticoagulants (NOACs) are currently the anticoagulants of first choice.[1] These drugs are non-inferior to vitamin K antagonist (VKA) treatment with respect to mortality, bleeding, and thromboembolism, show a significant reduction in intracranial bleeding, and have the benefit of not requiring routine laboratory monitoring as is needed with VKAs. However, NOACs do require dose adjustment based on patient characteristics including renal function, weight, and age.

Despite clear dosing recommendations, off-label dosing of NOAC is frequently reported.[2–6] Real-world patients are often different from patients enrolled in clinical trials, and as a result of individually balancing thrombosis and bleeding risk, there can be a valid rationale for deviating from the labelled dosing recommendation. However, it is unclear what the effect of non-recommended dose adjustments is on thrombosis and bleeding. Non-randomized studies suggest an increased rate of adverse events, but as selection bias has likely influenced results, these studies should be interpreted with caution.[2–4,7]

Nonetheless, given the potential for an increased risk of bleeding with overdosing and thrombosis with underdosing, it is of importance to identify determinants of such off-label use. This could help our understanding on how the safety of NOAC use in contemporary practice may be improved. Although the body of literature on off-label dosing in NOAC recipients is increasing, prospective studies evaluating label adherence to NOAC dosing at the initiation of AF treatment are scarce, yet of great importance, because this is the moment physicians make a critical first choice for the type of NOAC and its dose. Moreover, most current studies relied on retrospective healthcare registries or claims data, thus inherently suffering from misclassification or missing data for important variables, such as body weight or renal function.

Therefore, this study sought to determine the frequency of contemporary off-label dosing in newly diagnosed AF patients receiving their initial NOAC prescription, using data from a nationwide prospective and harmonized data collection registry of AF patients in the Netherlands. Moreover, determinants of such off-label dosing were explored.

Methods

In the prospective DUTCH-AF registry, patients with AF or atrial flutter aged ≥18 years were eligible for inclusion if AF or atrial flutter was diagnosed within the previous 6 months. Excluded were patients with (i) moderate or severe mitral valve stenosis, (ii) mechanical valve(s), (iii) a life expectancy of <6 months, or (iv) patients in whom AF or atrial flutter was only documented within 2 weeks following cardiothoracic surgery. Enrolment started in July 2018, and data available up till November 2020 were used. DUTCH-AF also incorporates a subsample of AF patients in whom retrospectively data were gathered from the already existing Netherlands Heart Network. These patients were diagnosed earlier with AF in the period November 2014 to December 2018, and they were prospectively followed after informed consent was obtained. The inclusion and exclusion criteria of these patients were the same as for the other participants in the DUTCH-AF registry, as were the gathered patient characteristics. The design of the DUTCH-AF registry was reported previously.[8]

For the primary analyses, only patients who were prescribed a NOAC and in whom label adherence could be assessed were included. Label adherence to NOAC dosing was determined by comparing the prescribed dose at diagnosis with the recommended dose based on age, weight, and/or renal function, as mentioned in the respective summaries of product characteristics from the European Medicines Agency (EMA) (see Supplementary material online, *Table S1* for an overview).[9] Overdosing was defined as the prescription of a full-dose NOAC (i.e. dabigatran 150 mg, rivaroxaban 20 mg, apixaban 5 mg, or edoxaban 60 mg) in patients with a dose-reduction recommendation according to the labelled criteria. Underdosing was defined as the prescription of a reduced dose NOAC (i.e. dabigatran 110 mg, rivaroxaban 15 mg, apixaban 2.5 mg or edoxaban 30 mg) in patients with no dose reduction recommendation according to the labelled criteria.[9] In the Netherlands, the Cockroft–Gault formula as used in the pivotal NOAC trials to estimate creatinine clearance is almost never used in daily clinical practice. Therefore, creatinine clearance was calculated using the widely used CKD-EPI formula.[10] The sponsor and coordinating centre of DUTCH-AF is Leiden University Medical Centre, and the study is registered at the Netherlands Trial Register (NL7464). Data management was overseen by the Netherlands Heart Registration.

Statistical analysis

Categorical variables are described as numbers (%), and continuous variables as mean ± standard deviation. A *t*-test or Mann–Whitney U-test was performed for comparison of continuous variables, depending on the normal distribution. To explore determinants for off-label dosing, patients were categorized into two subgroups: (i) patients with a full-dose recommendation, comparing full-dose NOAC prescribed on-label vs. reduced dose NOAC prescribed off-label (i.e. underdosed) and (ii) patients with a reduced dose recommendation, comparing reduced dose NOAC

prescribed on-label vs. full-dose NOAC prescribed off-label (i.e. overdosed). Patient characteristics possibly related to over- or underdosing were selected based on previous studies and clinical relevance, including age, renal function, weight, characteristics from the CHA_2DS_2-VASc score and characteristics associated with bleeding risk (see Supplementary material online, *Table S2* for a full overview). Only characteristics that are univariably associated with off-label dosing are displayed in *Tables 2 and 3*. Next, multivariable logistic regression was performed to assess the individually adjusted odds ratios (ORs). Variables were checked for non-linearity and interaction. Odds ratios are presented with 95% confidence intervals (CIs). A two-tailed *P*-value of <0.05 was considered significant. As missing data was uncommon (see Supplementary material online, *Table S3*), a complete case analysis was performed. Analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (Armonk, NY: IBM corp.).

Results

In total, 4500 patients from 22 hospitals, 5 anticoagulation clinics and 18 primary care practices were enrolled in DUTCH-AF, of whom 3588 (79.7%) patients were enrolled prospectively. The mean age was 69.6 ± 10.5 years and 1867 (41.5%) were female. The mean CHA_2DS_2-VASc stroke risk score was 2.7 ± 1.6, and 5.9% of patients were classified as high risk of bleeding according to the HAS-BLED bleeding risk score (score ≥3).[11,12] The most common comorbidities were hypertension (55.7%), diabetes mellitus (14.2%), and coronary artery disease (13.7%) (*Table 1*). At diagnosis, 3440 (76.4%) of 4500 patients were prescribed NOACs, and 317 (7.0%) VKAs (*Table 1*). The most common NOAC prescribed was apixaban (31.0% of NOAC users), followed by rivaroxaban (22.7% of NOAC users). Antiplatelet monotherapy was prescribed in 128 (2.8%) patients, and 582 (12.9%) patients were not treated with antithrombotics. Combination therapy of antiplatelets with OAC was prescribed in 120 (2.7%) patients.

Table 1 Patient characteristics at diagnosis

Variable	*N* = 4500	Missing
Female sex	1867 (41.5)	0 (0.0)
Age, years	69.6 ± 10.5	0 (0.0)
≥80 years	715 (15.9)	
Weight, kg	85.1 ± 18.2	331 (7.4)
<60 kg	226 (5.4)	
Comorbidities		
Congestive heart failure	267 (6.0)	41 (0.9)
Hypertension	2495 (55.7)	23 (0.5)
Diabetes mellitus	638 (14.2)	5 (0.1)
Ischaemic stroke or TIA	495 (11.0)	19 (0.4)
Venous thromboembolism[a]	181 (4.1)	40 (0.9)
Coronary artery disease[b]	614 (13.7)	6 (0.1)
Peripheral artery disease	246 (5.5)	34 (0.8)
Anaemia[c]	526 (12.7)	356 (7.9)
CrCl, ml/min/1.73 m^2	74.0 ± 18.3	239 (5.3)
<50 ml/min/1.73 m^2	426 (10.0)	
History of bleeding	80 (1.8)	42 (0.9)
Active malignancy	156 (3.5)	24 (0.5)
Risk scores		
CHA_2DS_2-VASc[12]	2.7 ± 1.6	111 (2.5)
Low risk (male: 0, female: 1)	537 (12.2)	
Intermediate risk (male: 1, female: 2)	943 (21.5)	
High risk (male: ≥2, female: ≥3)	2909 (66.3)	
HAS-BLED[d,11]	1.1 ± 0.9	569 (12.6)
Low risk (0–2)	3701 (94.1)	
High risk (3–6)	230 (5.9)	
Antithrombotics at diagnosis		0 (0.0)
None	582 (12.9)	
NOAC	3440 (76.4)	
Dabigatran	749 (16.6)	
Rivaroxaban	1020 (22.7)	
Apixaban	1397 (31.0)	
Edoxaban	274 (6.1)	
VKA	317 (7.0)	
Acenocoumarol	252 (5.6)	
Phenprocoumon	65 (1.4)	
Other (e.g. heparin)	33 (0.7)	
Antiplatelet monotherapy	128 (2.8)	
OAC concomitant with antiplatelets	120 (2.7)	

Categorical data are presented as *n* (%) and continuous data as mean ± standard deviation.
CrCl, creatinine clearance; NOAC, non-vitamin K oral anticoagulant; OAC, oral anticoagulant; TIA, transient ischaemic stroke; VKA, vitamin K antagonist.
[a]History of pulmonary embolism or deep venous thrombosis.
[b]History of myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting.
[c]Haemoglobin in mmol/L of <8.1 in males, <7.5 in females.
[d]Calculated without availability of liver function, international normalized ratio, concomitant use of non-steroidal anti-inflammatory drugs or alcohol use.

Label adherence

Of the 3440 patients treated with a NOAC, four patients had a contraindication for NOAC use due to a severely impaired renal function. In 184 patients, NOAC label adherence could not be determined due to missing variables, most often a missing recent renal function (141 of 184 patients). Of the remaining 3252 patients, a full-dose NOAC was prescribed in 2858 patients (87.9%) and a reduced dose NOAC in 394 (12.1%) patients. In total, 212 (6.5%) received their NOAC dose off-label, of which 77 (2.4%) were overdosed and 135 (4.2%) were underdosed (*Figures 1 and 2*).

Underdosing

Of the 2916 (89.7%) patients with a recommendation for a full-dose NOAC, 135 (4.6%) were underdosed. This proportion was comparable between the four NOACs, ranging between 3.6% for edoxaban and 5.1% for apixaban (*Figure 2*). Compared with patients using a full-dose NOAC on-label, underdosed patients were older (75.3 ± 9.0 vs. 69.1 ± 8.9 years, $P < 0.001$) and had an overall higher predicted risk of stroke (CHA_2DS_2-VASc 3.3 ± 1.4 vs 2.7 ± 1.5, $P < 0.001$) and bleeding (HAS-BLED 1.6 ± 0.8 vs 1.1 ± 0.8, $P < 0.001$). Characteristics that had a univariable association with underdosing are displayed in *Table 2*. After multivariable analysis, higher age, lower renal function, lower weight, active malignancy, anaemia, and concomitant use of antiplatelets were significantly associated with underdosing (*Table 2*).

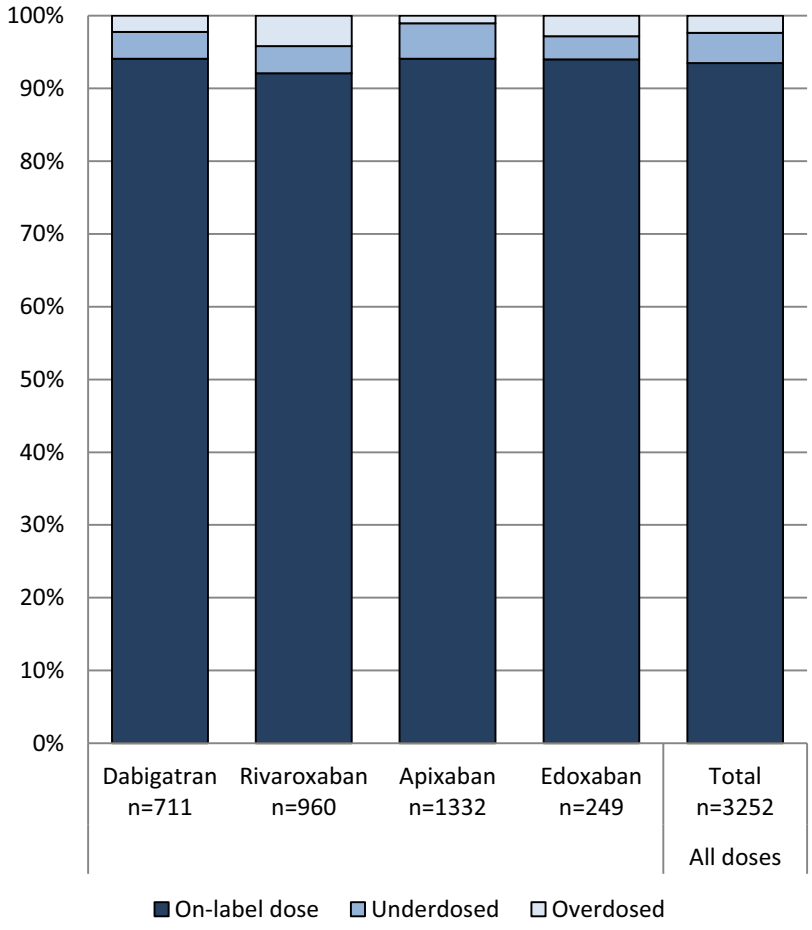

Figure 1 Label adherence per NOAC.

Overdosing

Of the 336 (10.3%) patients with a recommendation for a reduced dose NOAC, 77 (22.9%) were overdosed. This proportion varied between the four NOACs, ranging from 9.2% for dabigatran to 25.9% for edoxaban, 28.6% for apixaban, and 46.5% for rivaroxaban (*Figure 2*). Compared with patients using a reduced dose NOAC on-label, overdosed patients were younger (76.7 $\pm$ 8.9 vs 80.9 $\pm$ 5.9 years, $P <$ 0.001) and had an overall lower predicted risk of stroke (CHA_2DS_2-VASc 3.5 $\pm$ 1.5 vs 4.1 $\pm$ 1.3, $P = 0.001$) but a comparable predicted risk of bleeding (HAS-BLED 1.4 $\pm$ 0.6 vs. 1.6 $\pm$ 0.7, $P =$ 0.11). Characteristics which had a univariable association with overdosing are displayed in *Table 3*. After multivariable analysis, lower age and lower renal function were significantly associated with overdosing (*Table 3*).

Discussion

This study was performed to explore the extent and determinants of off-label NOAC dosing in newly diagnosed patients with AF. Our findings show that label adherence to NOACs was high, and only 2.4% and 4.2% of NOAC users were over- and underdosed, respectively. Given that in these NOAC users, only a small subset is in need of NOAC dose reduction; overdosing was uncommon overall; yet, more than one-fifth of patients with a recommendation for a reduced dose received a full dose. The proportion of patients who were underdosed was similar between NOACs, but a significant variation between NOACs was observed in overdosed patients, most often in rivaroxaban. Patient characteristics associated with off-label dosing—either overdosing or underdosing—were age and renal function, whereas for underdosing, weight, anaemia, active malignancy, and concomitant use of antiplatelets were independent determinants.

The low proportion of off-label NOAC dose prescription in the Netherlands has previously been observed in smaller Dutch cohort studies. Data from a single-centre study on 3231 NOAC naïve AF patients from the Netherlands showed only marginally higher proportions compared with our observations (4.5% overdosed and 5.4% underdosed).[2] In addition, in the worldwide GARFIELD-AF registry that registered patients with newly diagnosed AF and one or more risk factors for stroke, the Dutch cohort had a similarly low rate of off-label dosing. This was in contrast to the worldwide GARFIELD-AF cohort, which reported 3.8% overdosing and 23.2% underdosing among all AF patients on NOAC.[7] In the ORBIT-AF II registry, which enrolled US patients with recent-onset AF and novel NOAC therapy, 3.4% of NOAC users were overdosed and 9.4%

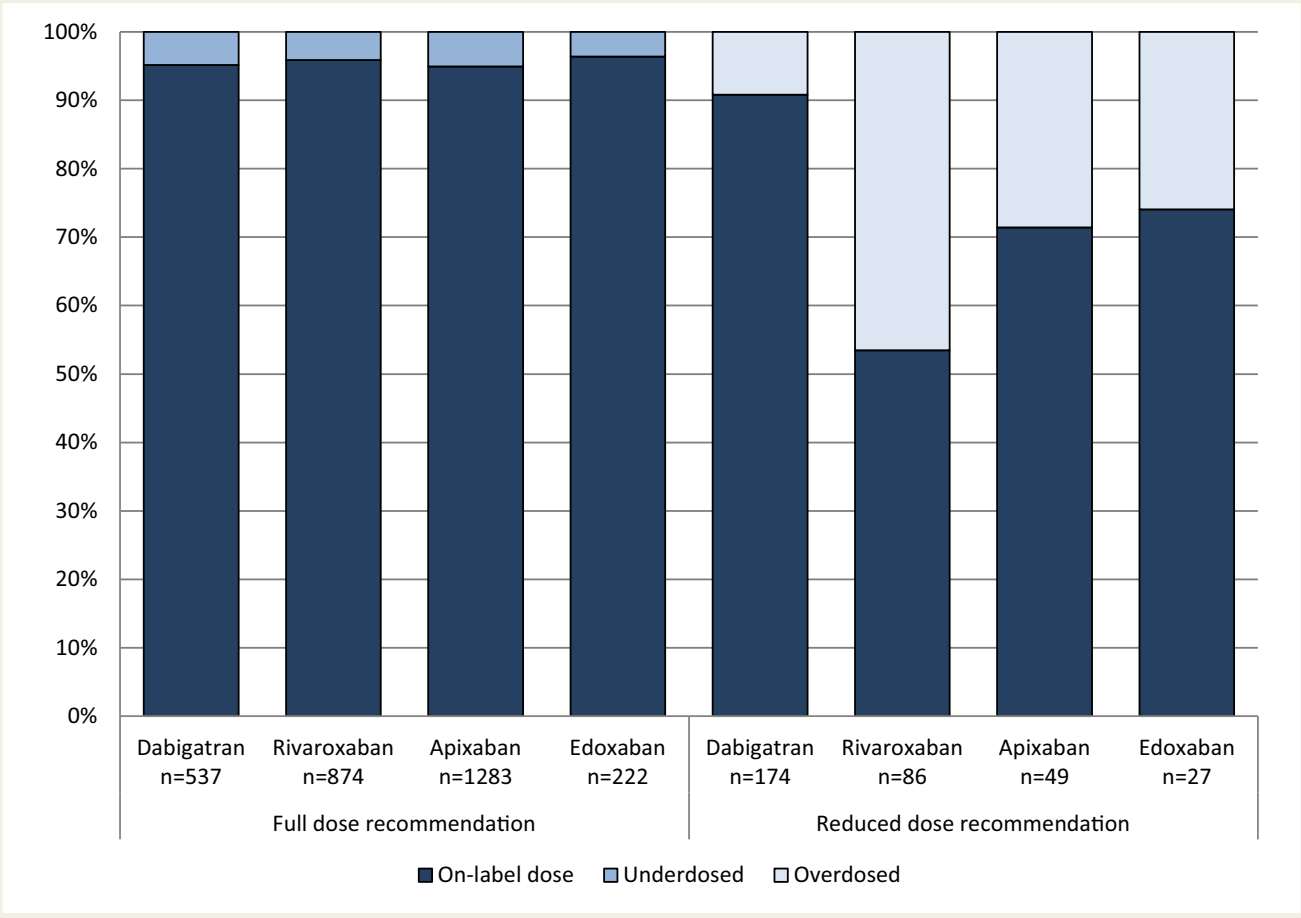

Figure 2 Label adherence per NOAC based on dose recommendation.

Table 2 Patient characteristics associated with underdosing of NOACs

	On-label full dose	Off-label reduced dose	Unadjusted		Adjusted	
	N = 2781	*N* = 135	Odds ratio	*P*-value	Odds ratio	*P*-value
Age, years	69.1 ± 8.9	75.3 ± 9.0	1.10 (1.07–1.12)	<0.001	1.01 (1.01–1.02)	<0.001
CrCl, ml/min/1.73 m^2	76.5 ± 15.1	63.1 ± 19.3	0.95 (0.94–0.96)	<0.001	0.96 (0.91–0.98)	<0.001
Weight, kg	86.2 ± 18.0	79.5 ± 16.7	0.98 (0.97–0.99)	<0.001	0.98 (0.97–1.00)	0.008
Coronary artery disease	355/2777 (12.8)	29/135 (21.5)	1.87 (1.22–2.86)	0.004	1.09 (0.63–1.88)	0.77
Peripheral artery disease	131/2764 (4.7)	12/133 (9.0)	1.99 (1.07–3.70)	0.03	1.26 (0.63–2.51)	0.52
Active malignancy[a]	84/2767 (3.0)	10/134 (7.5)	2.57 (1.30–5.07)	0.01	4.25 (1.58–11.42)	0.004
Anaemia[a]	257/2660 (9.7)	32/130 (24.6)	3.05 (2.01–4.64)	<0.001	1.67 (1.00–2.82)	0.05
OAC concomitant with antiplatelets	60/2781 (2.2)	16/135 (11.9)	6.10 (3.41–10.90)	<0.001	4.28 (1.99–9.17)	<0.001

Underdosing according to EMA labelling. Categorical data are presented as *n* (% of total) and continuous data as mean ± standard deviation. Odds ratios are displayed with 95% confidence intervals, for continuous variables per unit increase.
[a]Significant interaction between anaemia and active malignancy, $P = 0.04$.
CrCl, creatinine clearance.

underdosed.[5] A large, cross-sectional study from the U.K., which included patients with AF and a novel prescription of NOAC, showed overdosing as high as 16.9% with dabigatran and underdosing as high as 21.6% with apixaban.[3] Overall, off-label NOAC dosing in AF, including not newly diagnosed AF, seems to range between 25 and 50% globally.[4] The reasons for the low off-label use of NOACs in the Netherlands cannot be derived from this substudy. However, we postulate that it is possibly a result of high awareness of the issue.

Table 3 Patient characteristics associated with overdosing of NOACs

	On-label reduced dose	Off-label full dose	Unadjusted		Adjusted	
	N = 259	*N* = 77	Odds ratio	*P*-value	Odds ratio	*P*-value
Age, years	80.9 ± 5.9	76.7 ± 8.9	0.92 (0.89–0.96)	<0.001	0.93 (0.89–0.96)	<0.001
CrCl, ml/min/1.73 m^2	57.6 ± 17.9	51.4 ± 17.6	0.98 (0.97–1.00)	0.008	0.98 (0.97–1.00)	0.03

Overdosing according to EMA labelling. Categorical data are presented as *n* (% of total) and continuous data as mean ± standard deviation. Odds ratios are displayed with 95% confidence intervals, for continuous variables per unit increase.
CrCl, creatinine clearance.

This could in part be secondary to the public discussion on the safety of the NOACs, which arose around 2012 in the Netherlands when these drugs were introduced, which could have increased overall awareness. We hypothesized that there could be a difference in awareness of this issue between primary care and secondary/tertiary care. However, no difference between off-label dosing was seen between these different levels of care, and moreover, the proportion of patients treated with an off-label dose did not vary greatly between different including centres (Supplementary material online, *Table S4* and *Figure S1*). Moreover, it is our experience that Dutch pharmacies help check if NOACs are dosed according to the label, as pharmacies often have access to the patients' latest renal function, as well as weight, age, and comedication. In addition, differences in case mix and a study effect could have been of influence.

Notably, the proportion of overdosing among patients with a reduced dose recommendation was high. Overdosed patients had on average a lower age and a lower renal function. The reason herefore remains speculated, but an instance where this could occur is in patients with impaired renal function and an indication for dose reduction (such as with edoxaban or rivaroxaban). If this patient is relatively young, the prescribing physician could have deliberately chosen to overdose the patient given a (perceived) low bleeding risk. The lowest rate of overdosing was seen for dabigatran, which is to be expected, given the non-absolute dosing criteria for this NOAC, as physicians are free to choose between the 150 mg and 110 mg dose of dabigatran in selected patients (see Supplementary material online, *Table S1*).[9] Moreover, age ≥80 years is the only criteria included in our analysis for which a dose reduction is recommended in dabigatran, which is an easier dosing criterion than renal function or weight which are more variable. Overdosing was more often seen in patients initiated on a Factor Xa-inhibitor, in which 61 of 162 (37.7%) patients with a recommendation for using a reduced dose were overdosed. In patients using apixaban, it could be hypothesized that the more complex dosing criteria—in which 2 of 3 criteria must be present to justify dose reduction—could result in more off-label dosing. However, overdosing was similar to edoxaban and less than in rivaroxaban that has more straightforward dosing criteria. The reasons for this relatively high proportion of overdosing cannot be determined from this study, but it might be in part due to an unintentional dosing error. Although it is true that the vast majority (89.7%) of NOAC-eligible patients should be prescribed a full-dose NOAC according to the dosing criteria, it is of importance to always check the patient's age, renal function, and/or weight to see whether the dose adjustment is needed.

In previous studies as in this study, underdosing of NOACs is more common than overdosing.[2–7] The type of NOAC does not seem to matter, as no clear variation in underdosing between the different NOACs was observed in this study. The most important determinants associated with underdosing are factors associated with an increased bleeding risk, i.e. anaemia, an active malignancy, and concomitant use of antiplatelets, besides higher age, lower renal function, and lower weight. In patients with a high predicted bleeding risk, the choice between on-label vs. off-label dosing can be difficult, as the phase III trials in which the dosing criteria were validated largely excluded such patients. Moreover, the stroke risk in patients with an increased intrinsic risk of bleeding is often high too. Given these uncertainties, it is still uncertain whether some patients seen in clinic, who are deemed to be at high risk of bleeding, would be better served with an on- or off-label NOAC prescription. Importantly, however, previous observational studies have shown that off-label reduced dosing of NOACs, in general, is associated with more cardiovascular hospitalization, mortality, and thrombosis, without an apparent reduction in major bleeding compared with on-label dosing.[5,7] Of note, these results should be interpreted with caution as selection bias and unblinded assessment of outcomes may have occurred.

A pooled *post hoc* analysis of the pivotal NOAC trials reported 31% more major bleeds in patients using a NOAC concomitant with an antiplatelet agent vs. NOAC monotherapy.[13] Therefore, combining a reduced NOAC dose concomitant with antiplatelet therapy seems intuitive to lower bleeding risk but inherently could increase stroke risk. The vast majority of patients in DUTCH-AF receiving antiplatelet therapy had undergone coronary revascularization. Evidence regarding the effectiveness and safety of reducing NOAC dose in the presence of antiplatelet therapy after percutaneous coronary intervention (PCI) in AF mainly comprised the RE-DUAL PCI and PIONEER AF-PCI trials.[14,15] In the RE-DUAL PCI trial, dabigatran 110 mg b.i.d. plus a $P2Y_{12}$ inhibitor regimen resulted in significantly lower bleeding rates than dabigatran 150 mg b.i.d. plus a $P2Y_{12}$ inhibitor, or warfarin plus dual antiplatelet therapy.[14] In the PIONEER AF-PCI trial, rivaroxaban 15 mg o.d. plus a $P2Y_{12}$ inhibitor also resulted in significantly lower bleeding rates compared with warfarin plus dual antiplatelet therapy, whereas a rivaroxaban 20 mg cohort was not included.[15] Based on these trials, the 2020 AF guideline from the European Society of Cardiology recommends that a reduced dose of dabigatran or rivaroxaban concomitantly with a $P2Y_{12}$ inhibitor after PCI may be considered in patients with a high bleeding risk (i.e. HAS-BLED ≥3).[1] Although the 2020 ESC AF guidelines were published at the end of our study observation period, physicians could have already implemented the results of the RE-DUAL PCI and PIONEER AF-PCI trials into their practices. It should be noted however that both trials were underpowered to detect the observed between-group differences in

their efficacy endpoints. Therefore, reducing the NOAC dose outside of the EMA labelling when antiplatelet therapy is initiated should always be carried out with caution.

Strengths and limitations

A major strength of this study is that a large cohort of patients from different levels of care, including academic and non-academic hospitals (both out- and inpatients), primary outpatient clinics, as well as outpatient anticoagulant clinics, were prospectively enrolled. Our cohort is therefore likely an accurate reflection of Dutch everyday AF practice. Moreover, our contemporary data was registered at diagnosis, and the initial choice regarding antithrombotic therapy was recorded.

The most important limitations of this study are those related to the observational and pragmatic design of this registry. For example, data on the use of strong P-glycoprotein inhibitors or other drugs included in the labelled dosing criteria of the individual NOACs were not collected, which could have resulted in misclassification of label adherence. Another limitation is the inclusion of retrospectively collected data in 912 patients from this cohort. In addition, as patients were prospectively enrolled, physicians could have been aware of (possible) study participation, which could have resulted in extra awareness and therefore less off-label dosing.

Conclusion

In newly diagnosed Dutch AF patients, off-label dosing of NOACs was seen in only 6.6% of the patients, most often underdosing. In this study, determinants of off-label dosing were age, renal function, weight, anaemia, active malignancy, and concomitant use of antiplatelets.

Lead author biography

Jaap Seelig earned a medical degree from the Radboud University, Nijmegen, the Netherlands. He is currently a PhD student of the Maastricht University, with his research focusing on the contemporary quality of anticoagulation management in atrial fibrillation. He is currently in training to become a cardiologist at the Radboud University Medical Centre.

Data availability

The data underlying this article are available in the article and in its Supplementary material online.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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Ethics approval

The study complies with the Declaration of Helsinki, and the research protocol was reviewed and approved by the ethics committees of all participating centres.

Consent

Informed consent was obtained from participants, aside from patients in some centres in which informed consent was waived by the local ethics committee due to the observational nature of the registry with no risks involved for patients.

Author contributions

J.S. drafted the manuscript together with G.C., E.M.T.-R., T.A.C.d.V., G.J.G., F.H.R., M.E.W.H., and M.V.H. M.E.W.H. and M.V.H. are the principal investigators of DUTCH-AF. All authors contributed to and approved the final manuscript.

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